

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

AM

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/557	A1	(11) International Publication Number: WO 96/09825 (43) International Publication Date: 4 April 1996 (04.04.96)
(21) International Application Number: PCT/GB95/02277 (22) International Filing Date: 26 September 1995 (26.09.95) (30) Priority Data: 9419566.6 27 September 1994 (27.09.94) GB (71) Applicant (for all designated States except US): UNIVERSITY COLLEGE LONDON [GB/GB]; Gower Street, London WC1E 6BT (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): EL-REFAEY, Hazem [EG/GB]; 62A Prince of Wales Mansions, Prince of Wales Drive, London SW11 4BJ (GB). (74) Agents: STEBBING, Peter, John, Hunter et al.; Ablett & Stebbing, 45 Lancaster Mews, Lancaster Gate, London W2 3QQ (GB).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PROSTAGLANDIN ANALOGUES BY THE ORAL OR VAGINAL ROUTE FOR THE ROUTINE MANAGEMENT OF THE THIRD STAGE OF LABOUR (57) Abstract The invention relates to the utilisation of a prostaglandin analogue by the oral or vaginal route for the routine management of the third stage of labour. The invention shows that the use of a prostaglandin, particularly Misoprostol gives excellent results in the prevention of postpartum haemorrhage (PPH) when routinely administered immediately postpartum at 400-600 µg.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Larvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

PROSTAGLANDIN ANALOGUES BY THE ORAL OR VAGINAL ROUTE
FOR THE ROUTINE MANAGEMENT OF THE THIRD STAGE OF LABOUR

The present invention relates to the use of an alternative
5 pharmaceutical agent in the place of Syntometrine and
ergometrine for routine prevention of bleeding during or
immediately after the third stage of labour. It is generally
accepted that the advantages of the use of the aforementioned
drugs outweigh their disadvantages and hence they are
10 routinely administered to all women in Europe and North
America immediately after delivery unless specifically
contraindicated. No equally effective acceptable alternative
has been introduced to the obstetric practice since these
drugs were first described almost 60 years ago. I have found
15 that Misoprostol, a drug that is widely marketed for the
treatment of stomach ulcers, can fulfil the requirements of
an effective agent that can be used routinely for that
purpose.

20 The third stage of labour is potentially the most hazardous
part of labour for the mother. The main risk is that of
postpartum haemorrhage (PPH) with its subsequent morbidity.
The rise of oxytocic drugs for the prevention of PPH has been
regarded as one of the most enduring advances in medical
25 science. The intramuscular administration of syntometrine (a
combination of 5 i.u. syntocinon with 0.5 mg of Ergometrine)
after the delivery of the fetus is widely practised in the
developing world and has become known as the active management
of the third stage of labour.

30

The prophylactic use of oxytocics in the third stage of labour
is of particular relevance to obstetrics practice in the third
world where atonic postpartum haemorrhage is a common event
due to high multiparity, prolonged labour and fibroid uterus.
35 Maternal death due to PPH is reported to be between 17 and 40%
in some parts of the world (World Health Organisation 1989 and

1991). Postpartum haemorrhage is the single most common cause of maternal death in the developing world.

The concept of actively managing the third stage of labour, like many other interventions in the managements of labour, has been challenged in recent years. The first large randomised study performed in this field has shown that the routine use of syntometrine in the third stage of labour has been shown to reduce the incidence of PPH from around 18% to 5% and to reduce the length of the third stage of labour from fifteen minutes to five minutes. Further, it has been shown to reduce the need for therapeutic oxytocics from 30% to 6%. An overview of trials performed in this field strongly suggests that the routine prophylactic use of an oxytocic in the third stage of labour reduces the incidence of PPH. Despite this important problems remain.

Syntometrine is an effective combination administered by the intramuscular route, the syntocinon acting in about 2.5 minutes and the Ergometrine producing a more sustained uterotonic contraction five minutes later. However, Syntometrine is contraindicated in women with high blood pressure in pregnancy. An estimated 15% of women are therefore denied the beneficial effects of Syntometrine in the third stage of labour.

The advantages of using Syntometrine must be considered with the rare but serious side effects attributed to their hypertensive properties. Syntometrine has been known to produce a rise in blood pressure in women previously known to be normotensive. Maternal death from cardiac arrest and intracerebral haemorrhage have been attributed to Ergometrine, as have non-fatal instances of cardiac arrest and myocardial infarction. Syntometrine has also been known to be commonly associated with gastrointestinal side effects in the form of nausea and vomiting which can reduce patient acceptability.

Active management of a third stage of labour is not a universal practice. In many parts of the world, the routine use of oxytocic agents is not a practical option for various other reasons. First, oxytocic agents are not stable at high ambient temperatures and therefore require special storage requirements, for example refrigeration, over prolonged periods, Syntometrine has to be stored between 2° and 8°C and protected from light. Although Syntometrine may be stored at temperatures up to 25°C for two months when protected from light, activity tends to decline. One study investigated the stability of Ergometrine and Methyl Ergometrine after one year of suboptimal storage which showed that 90% of the therapeutic activity of the drugs was lost over that period. The results are similar when the drug is stored in brown vials.

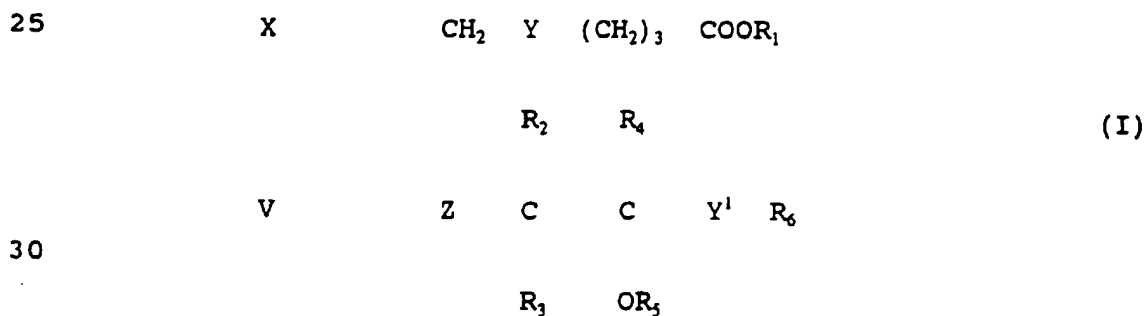
These requirements represent an important hurdle to the wider use of oxytocics in the developing world and accordingly, the feasibility of synthesizing forms of the drugs which are able to withstand high temperatures was considered by the World Health Organisation, (WHO) without a successful candidate being available to date.

Secondly, active management of the third stage of labour is also compromised in the third world situations because of the unknown status of the mother. Often mothers present to clinics in an advanced stage of labour when the doctor is unable to assess the likely hitherto hypertensive status of the mother and indeed is likely to be faced with difficult decisions of a more immediate nature. Because of this, oxytocics are not routinely administered, even if available in case their administration exacerbates latent hypertension.

Further, the prevalence of Hepatitis C, AIDS and other blood born diseases, in third world countries means that drugs are administered by injection only if there is no practical alternative.

Accordingly in order to find a suitable replacement for active management of the third stage of labour, a drug must have the following properties.

- 5 1. Storable at ambient temperatures with a long shelf-life.
2. Capable of stopping bleeding postpartum at low dosages and without significant side effects.
- 10 3. Having a rapid onset action.
4. Administrable by the oral or vaginal route so as to be routine for prophylaxis.
- 15 5. Have the same or an enhanced efficacy with regard to prevention of PPH and
6. Non-hypertensive or better still slightly hypotensive.
- 20 Misoprostol originally formed the subject of GB-A-1492426 which relates to synthetic 15-deoxy-16-hydroxy-16-methyl analogues of naturally occurring prostaglandin E1⁵, of the formula (1)



wherein R₁, R₂ and R₃ are hydrogen or an alkyl radical containing from 1 to 7 carbon atoms; R₄ is an alkyl radical
 35 containing from 1 to 7 carbon atoms; R₅ is hydrogen, an alkyl radical containing from 1 to 7 carbon atoms or an alkanoyl radical containing from 1 to 7 carbon atoms; R₆ is an alkyl

5

radical containing from 2 to 4 carbon atoms or a cycloalkyl radical containing from 5 to 7 carbon atoms; X is carbonyl or hydroxymethylene; V is methylene, hydroxymethylene or alkanoyloxymethylene wherein the alkanoyl radical contains from 1 to 7 carbon atoms; or, when X is carbonyl, V may also be a radical of the formula



10 in which the bond represented by the dotted line in the general formula is present; Y is ethylene or vinylene; Y' is vinylene, ethynylene or the group



20

wherein n is 0 or 1 and R₇ and R₈ are hydrogen or an alkyl radical containing from 1 to 7 carbon atoms; Z is ethylene, vinylene or ethynylene; the wavy lines represent the alternative α or β stereochemical configuration or the epimeric mixture.

25

Our invention relates therefore to orally or vaginally administered prostagladins which have significant uteronicity without adverse side effects, are rapidly absorbed orally or from a suppository via the vaginal route, are quick acting and thermostable in storage. Drugs of this type of which the prostagladin E1⁵ analogues are preferred examples are particularly efficacious, Misoprostol itself is merely the most preferred.

35

Misoprostol is available under the tradename Cytotec and has been known for several years for oral administration for the healing of duodenal and gastric ulcers; including those induced by non-steroidal anti-inflammatory drugs; (NSAID).

Cytotec protects gastroduodenal mucosa by inhibiting basal, stimulated and nocturnal acid secretion; by reducing the volume of the secretion, by reducing proteolytic activity of the gastric fluid, and by increasing bicarbonate and mucosal
5 secretion.

Cytotec is contraindicated in pregnancy because it may cause intermenstrual bleeding in pre-menopausal women. The normal oral dose is 200 μ g, four times a day, for use in ulcer
10 therapy. Preclinical animal studies have shown that the drug had no effect on the uterus. However, Misoprostol has been used, without the benefit of medical intervention, in very large doses per os in Latin America as an abortifacient and lately its uterine effects have been discussed.
15 Prostaglandins in general have been used in obstetrics for at least two decades and are widely used, often with other agents, for cervical ripening, induction of labour and induction of abortion. Some injectable prostaglandins have also been used as a last resort in the treatment of critically
20 ill patients with intractable postpartum haemorrhage.

~~A prostaglandin-F₂A has in fact already been used in one trial~~
in 1979 to assess the efficacy of its prophylactic use in the third stage of labour. As this prostaglandin can only be
25 administered by direct injection into the uterine muscle (intramyometrially) it is inappropriate to recommend such an invasive approach for general use. Further, this group of prostaglandins is associated with unacceptable side effects such that its use is only suitable in life threatening
30 situations.

Misoprostol and its immediate analogues set out above, is an E1 prostaglandin analogue which may be administered orally. Its safety is well established in the prevention and
35 management of peptic ulcer disease.

Misoprostol has been shown in animal studies to possess a mild hypotensive effect at about 800 μ g in a single dose whereas at about 400 μ g, patients remain substantially normotensive.

5 As stated above, unlike oxytocic agents, I have now shown that Misoprostol and similar prostagladin analogues when administered to humans are not hypertensive up to dosages of 800 μ g and accordingly, by virtue of their strong uteronic features, they have an apparent superiority in the management
10 of postpartum haemorrhage and appear to be ideal agents for prophylactic use in the third stage in labour. With regard to Misoprostol in itself; Misoprostol is already marketed as tablets for oral use, does not require special storage conditions and is known to possess a shelf-life of several
15 years.

Accordingly therefore to the present invention there is provided the use in the manufacture of a drug for prophylactic treatment of mothers in the third stage of labour of an orally
20 or vaginally administrable active principal selected from a quick acting thermostable prostagladin analogue with significant uteronicity disposed in a pharmaceutically acceptable carrier or diluent therefor. In particular, this compound may be selected from a synthetic 15-deoxy-16-hydroxy-
25 16-methyl analogue of an naturally occurring prostagladin E₁ and particularly from a compound of the formula I given above for example Misoprostol.

In particular, this compound may be selected from racemic
30 methyl 7-[3(R)-hydroxy-2 β -(4(RS)-4-hydroxy-4-methyl-trans-1-octenyl)-5-oxocyclopentane]-1 α -heptanoate; racemic methyl 7-[3(S)-hydroxy-2 β -(4(RS)-4-hydroxy-4-methyl-1-octynyl)-5-oxocyclopentane]-1 α -heptanoate; and racemic methyl 7-[3(R)-hydroxy-2 β -(4(RS)-4-cyclohexylmethyl-4-hydroxy-4-methyl-trans-
35 1-butenyl)-5-oxocyclopentane]-1 α -heptanoate. The active principal may be administered orally in an amount of 200-800 μ g and preferably in an amount of about 400 or 600 μ g;

immediately after the second stage of labour. The diluent or carrier may be conventional and adapted to release the active principal to the contents of the stomach or intestine, or may be in the form of a suppository or pessary in accord with
5 normal pharmacological practice.

The active principal may be administrable orally in an amount of 100-800 μg and preferably in an amount of 400 to 600 μg as a single dose administered at the commencement of the third
10 stage of labour. The diluent or carrier may be any conventional diluent or carrier which is adapted to release the active principal sublingually into the contents of the stomach to achieve rapid onset. Misoprostol itself is particularly efficacious in the foregoing respects since
15 pharmokenetic studies have shown that Misoprostol under goes extensive metabolism during and/or prior to its gastro intestinal absorption. Several metabolites are formed and no unchanged drug is detected in the plasma or urine after use. The biologically active metabolite in the plasma is
20 Misoprostol acid, the absorption of Misoprostol and/or Misoprostol acid is extremely rapid resulting the peak plasma levels at less than fifteen minutes. The results are
substantially the same if the drug is administered vaginally.

25 The invention will now be described by way of illustration only in the following example:

Patients and Methods

The study protocol was reviewed and approved by the local
30 Ethics Committee. Information sheets explaining the aims of the trial were distributed to potential participants either in the antenatal classes, antenatal clinics, and the Day Assessment Area. On admission to labour ward women were reminded about the trial and a written informed consent was
35 obtained if they still wished to participate in the study.

The main objective of this study was to estimate the incidence of primary postpartum haemorrhage (PPH). This was defined as estimated blood loss of or more than 500 ml. Other measures of blood loss were also considered e.g. severe PPH i.e. > 1000 ml; secondary PPH (after 24 hours); need for blood transfusion; use of therapeutic oxytocics (i.e. the need for extra oxytocics); length of third stage; incidence of manual removal of placenta; the need for subsequent evacuation of the retained products of conception; and the change in haemoglobin and packed cell volume in those who had instrumental delivery and/or who had blood loss of 500 ml or more compared to the Haemoglobin done late in pregnancy. Potential adverse effects of the drug used were also recorded e.g. incidence of vomiting, diarrhoea, shivering and hypertension (defined as diastolic blood pressure > 100 or Systolic Blood pressure >150). All of these measures were documented by the midwife on call on a specially designed form with demographic information and information related to the type and circumstances of delivery.

20

The principle criteria for exclusion were: placenta praevia, multiple pregnancy, intrauterine death, gestational age less than 32 weeks gestation, women with previous PPH and women in their sixth pregnancy or more. In this pilot study, women with hypertension, preeclampsia or pregnancy induced hypertension were also excluded.

Immediately after delivery of the baby and clamping and dividing the cord, patients were asked to swallow 600 µg Misoprostol (3 tablets). Syntometrine was not given but midwives were instructed to do so if they felt there was a clinical indication. Otherwise the delivery of the placenta was managed according to hospital policy (active management policy). Blood loss was estimated clinically by the attendant midwife or obstetrician. A sample of venous blood was obtained two days later after birth for haemoglobin and packed cell volume assessment from women who had instrumental

delivery or from those who had blood loss of 500 ml or more. A record was kept of the last recorded blood pressure and temperature before birth and one hour after delivery.

5 Statistical Methods

Categorical variables are summarised as numbers and percentages, whereas continuous variables that are normally distributed are presented as means and standard deviations (SD), continuous variables that are not normally distributed are presented as medians and interquartile ranges (IQR). Comparisons between the systolic, diastolic blood pressure, haemoglobin, haematocrit and temperature before and after delivery were conducted via the paired t-test. Association between two categorical variables was assessed via Chi-square testing. The significance level was set to the 5% level.

Results

Two hundred and thirty seven patients with mean age (SD) of 29.1 (5.8) years, were recruited to the study. The demographic characteristics and labour variables of these patients are summarised in Table 1. One hundred and thirteen patients (48%) were primigravidae. 47 (20%) patients had induction of labour, whereas overall 72 (30%) required syntocinon augmentation. Episiotomy was performed for 52 (22%) patients. 107 (45%) patients had a 1st or 2nd degree tears. Epidural anaesthesia was used by 112 (47%) of these patients.

The placenta was delivered spontaneously in all cases apart from four cases (2%) where manual removal of the placenta was needed. The median length of the third stage of labour was 5 (IQR of 4 to 7) minutes). 13 (6%) patients had blood loss more than or equal to 500 ml of which only 6 (3%) had a blood loss greater than 500 whereas no patient had a blood loss of 1000 ml or more. Secondary post partum haemorrhage was not reported in any case. The median blood loss for all the study population was 200 (IQR of 150 to 300) ml. Four patients only

(2%) required a manual removal of placenta and four had a haemoglobin level of less or equal to 9 g/dl. Blood transfusion was required for 2 patients in this trial, one patient had a broad ligament haematoma that was managed conservatively. The second patient required blood transfusion during manual removal of a retained placenta. The effects of Misoprostol on the third stage of labour and its side effects are summarised in Table 2.

Gastrointestinal side effects were infrequent. Vomiting occurred in 19 (8%) patients during the first hour after delivery and loose stool was reported by seven (3%) patients during the first 24 hours after delivery. These were usually mild and did not necessitate any treatment. The occurrence of shivering was on the other hand reported by 148 (62%) patients. This was self-limiting and lasting for around 10-15 minutes twenty minutes are swallowing the tablets. There was no cases of infection and no patient required surgical evacuation of retained products of conception.

20

The last measured systolic and diastolic blood pressure before delivery was compared to that measured one hour after delivery. A mean reduction of 1.0 (SE = 0.9) and 0.8 (0.6) mm Hg respectively were observed but neither were statistically significant. Similarly, haemoglobin, haematocrit and temperature were compared before and after delivery. All are summarised in Table 3. A reduction of 0.3 (0.15) g/l of the haemoglobin and of 0.01 (0.005) of the haematocrit were marginally significant ($p=0.006$ and $p=0.047$). Temperature increased significantly by 0.5 (0.005) ($p=0.001$).

This report has shown that the third stage of labour can be successfully managed with Misoprostol. The incidence of postpartum haemorrhage (6%), need for further therapeutic oxytocics (5%) and the length of the third stage of labour (median 3 minutes) in this study is considerably lower than

those reported when the third stage is managed physiologically and comparable to that obtained by syntometrine. The success has been achieved with a simple oral medication.

- 5 The routine prophylactic administration of an oxytocic agent is an integral part of the active management of labour and has been shown to reduce the incidence of post partum haemorrhage from 18% to 5%, to reduce the length of the third stage of labour from 15 minutes to 5 minutes and the need for
10 therapeutic oxytocics from 30% to 6%. An overview of trials performed in this field strongly suggest that routine use of oxytocics in the third stage of labour reduces the incidence of PPH. The advantages of prophylactic syntometrine must be considered together with the rare but serious morbidity which
15 has been attributed to its hypertensive effect. The hypertensive effect was apparent when syntometrine was compared to Syntocinon; Syntometrine was found to increase the incidence of hypertension (diastolic blood pressure more than 100 mm/Hg) by 5 fold. Maternal death from cardiac arrest and
20 intracerebral haemorrhage have been attributed to this direct pharmacological effect, as have non-fatal instances of cardiac arrest and myocardial infarction. Due to the pilot nature of the present study, we excluded patients with high blood pressure from the trial, nevertheless we could not identify
25 any hypertensive effects of Misoprostol on women who were normotensive before labour.

- Women who express dissatisfaction with the conventional management of the third stage of labour report that vomiting
30 in particular is the most distressing symptom they had to endure. The incidence of vomiting reported in this study is almost half that reported when syntometrine is used. In this study, however we identified a side effect of Misoprostol that has not been described hitherto. Shivering occurred in 62%
35 of patients and was generally regarded as a nuisance rather than as a serious problem. In the field of abortion, the use of larger Misoprostol dosages was not associated with this

side effect. Its occurrence therefore was only identified during the prepilot work leading to this study. Shivering is a recognised symptom after normal delivery and its incidence increases in association with regional anaesthesia. During
5 epidural anaesthesia, the incidence of shivering is between 33-60%. This should be compared with an incidence of 10% during normal labour without epidural anaesthesia. In this study the incidence of shivering was 62%, there was no significant difference between patients who had epidural
10 anaesthesia and those who had not. It seems however that shivering is dose related and may be significantly reduced without loss of efficacy by reducing the dosage of active ingredient to 400 µg.

15 The prophylactic use of oxytocics in the third stage of labour is of particular relevance to the obstetric practice in the third world where atonic postpartum haemorrhage is a common event due to high multiparity, prolonged labour and fibroid uterus. Death due to postpartum haemorrhage is said to
20 represent between 17-40% of maternal mortality in some parts of the world. The availability of an oral and thermostable preparation for routine management of the third stage of
labour will have considerable implications for obstetric practice in developing countries. The implications are
25 considerable since if this approach became standard practice, the management of the third stage of labour would be simpler, potentially safer and more acceptable to women and their attendants alike everywhere.

TABLE 1
Demographic Characteristics and Labour Variables
of the Recruited Study Population

5		n = 237
	<u>Demographic variables:</u>	
	Mean (SD) maternal age (year)	29.1 (5.8)
	Mean (SD) maternal weight (kg)	76.3 (11.5)
	Mean (SD) maternal height (cm)	163.2 (6.7)
10	Number (%) of primigravidae	113 (48%)
	Mean (SD) of gestational age at delivery (week)	39.7 (1.4)
	<u>Labour variables:</u>	
	Number (%) with spontaneous onset	190 (80%)
15	Number (%) with Syntocinon augmentation	72 (30%)
	Number (%) with epidural in 1st or 2nd stage	112 (47%)
	Number (%) with narcotic analgesia in 1st or 2nd stage	90 (38%)
20	Number (%) with episiotomy	52 (22%)
	Number (%) with 1st, 2nd tear	106 (45%)
	Number (%) with Spontaneous cephalic delivery	179 (72%)
	Mean (SD) length of 1st stage (hour)	6.7 (3.9)
25	Mean (SD) length of 2nd stage (min)	66 (60)
	Mean (SD) of birthright (KG)	3.30 (0.5)

TABLE 2

Effect of Misoprostol on the Management of the Third Labour

		n = 237
5	Number (%) with blood loss \geq 500 ml	13 (6%)
	Number (%) with blood loss \geq 1000 ml	0 (0%)
	Median (IQR) of blood loss (ml)	200 (150-300)
	Number (%) with manual removal of placenta	4 (2%)
10	Number (%) with repeat syntometrine injection	12 (5%)
	Number (%) with systolic \geq 150 (mm Hg)	2 (1%)
	Number (%) with diastolic \geq 100 (mm Hg)	0 (0%)
	Number (%) with haemoglobin $<$ 9 (g/l)	4 (2%)
	Median (IQR) third stage length (min)	5 (4-7)
15	Number (%) with third stage length \geq 30 minutes	1 (0.5%)
	Number (%) who vomited	19 (8%)
	Number (%) who had diarrhoea	7 (3%)
20	Number (%) who had shivering	148 (62%)

TABLE 3

Maternal Blood Pressure, Haemoglobin and Temperature
Measurements Before and After Delivery

25

(Values are Means (SD))

		Before delivery	After delivery	Mean Difference (SE)	P-Value
30	Systolic blood pressure (mm Hg) n = 184	119.3 (13)	118.4 (12)	-1.0 (0.9)	0.25
30	Diastolic blood pressure (mm Hg) n = 184	73.8 (8)	73.0 (8)	-0.8 (0.6)	0.20
	Haemoglobin (g/l) n = 76	11.3 (0.9)	11.0 (1.3)	-0.3 (0.15)	0.06
35	Haematocrit n = 73	0.34 (0.03)	0.33 (0.04)	-0.01 (0.005)	0.047
	Temperature (C) n = 182	36.6 (0.4)	37.1 (0.7)	0.5 (0.05)	0.001

CLAIMS:

1. The use in the manufacture of a drug for prophylactic treatment of mothers in the third stage of labour for the limitation of postpartum haemorrhage (PPH) of an orally or vaginally administrable prostagladin analogue having a significant uteronicity without adverse side effects, which is rapidly absorbed orally or vaginally, is quick acting and thermostable in storage disposed in the pharmaceutically acceptable carrier or diluent therefor.
2. The use according to claim 1 wherein the prostagladin analogue is a synthetic 15-deoxy-16-hydroxy-16-methyl analogue of a naturally occurring prostagladin E1⁵.
3. The use according to claim 2 wherein the compound is selected from racemic methyl 7-[3(R)-hydroxy-2 β -(4(RS)-4-hydroxy-4-methyl-trans-1-octenyl)-5-oxocyclopentane]-1 α -heptanoate; racemic methyl 7-[3(S)-hydroxy-2 β -(4(RS)-4-hydroxy-4-methyl-1-octynyl)-5-oxocyclopentane]-1 α -heptanoate; and racemic methyl 7-[3(R)-hydroxy-2 β -(4(RS)-4-cyclohexylmethyl-4-hydroxy-4-methyl-trans-1-butenyl)-5-oxocyclopentane]-1 α -heptanoate.
4. The use of any preceding claim wherein the prostagladin is Misoprostol.
5. The use according to any preceding claim wherein the active principal is adapted for administration in an amount of 200 to 800 μ g
6. The use according to claim 5 wherein the amount is 400 to 600 μ g.

7. The use according to any preceding claims wherein the carrier or diluent is adapted to release the active principal sublingually into the contents of the stomach and/or gastro intestinal tract or wherein the carrier is in the form of a vaginal pessary or suppository.

INTERNATIONAL SEARCH REPORT

Intern: Application No

PCT/GB 95/02277

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	REV CHIL OBSTET GINECOL, vol. 59, no. 3, 1994 pages 190-196, G.A.CAMPOS ET AL. 'MISOPROSTOL-UN ANALOGO DE LA PGE1-PARA LA INDUCCION DE PARTO A TERMINO: ESTUDIO COMPARATIVO Y RANDOMIZADO CON OXITOCINA' see abstract	1-7
Y	OBSTET. GYNECOL., vol. 83, no. 2, February 1994 pages 244-247, H.FLETCHER ET AL. 'Intravaginal Misoprostol Versus Dinoprostone As Cervical Ripening and Labor-Inducing Agents' see abstract	1-7

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

20 February 1996

Date of mailing of the international search report

-1.03.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Theuns, H

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 95/02277

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	OBSTET. GYNECOL., vol. 83, no. 5pt1, May 1994 pages 799-801, L.SANCHEZ-RAMOS 'INTRAVAGINAL MISOPROSTOL VERSUS DINOPROSTONE AS CERVICAL RIPENING AND LABOR-INDUCING AGENTS' see the whole document ---	1-7
Y,P	BR.J.PHARMACOL., vol. 113, no. 2, October 1994 pages 369-374, Y.QIAN ET AL. 'Potent contractile actions of prostanoid EP3-receptor agonists on human isolated pulmonary artery' Introduction ---	1-7
Y	OBSTET. GYNECOL., vol. 81, no. 3, March 1993 pages 332-336, L.SANCHEZ-RAMOS ET AL. 'Labor Induction With the Prostaglandin E1 Methyl Analogue Misoprostol Versus Oxytocin: A Randomized Trial' see abstract ---	1-7
Y,P	AM.J.HOSP.PHARM., vol. 51, no. 19, 1 October 1994 pages 2394-2402-2504-2505, J.J.KELSEY ET AL. 'Drug therapy during labor and delivery' see page 2399 -----	1-7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB95/02277

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-2, 5-7
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The definition of chemical compounds by means of their biological/pharmaceutical profiles makes a complete search virtually impossible.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.